AMENDMENTS TO THE SPECIFICATION

Please amend the specification as follows.

At page 1, lines 13-16,

The present application claims priority from provisional application serial number 60/261,638, filed on January 12, 2001. ~~The present application is related to U.S. patents 5,885,956, filed December 14, 1992 and issued March 23, 1999, and 6,288,301 issued September 11, 2001, all of which are hereby incorporated by reference herein.~~

At page 3, line 24 to page 4, line 4:

In one embodiment, the invention provides a pharmaceutical composition including a synthetic gastrin derivative and a recombinant modified EGF. The ratio of the gastrin derivative to the recombinant modified EGF is about 60:1. Yet another embodiment is a pharmaceutical composition having a synthetic gastrin derivative having a leucine substituted at position 15, and a recombinant modified EGF having a deletion of two C-terminal amino acids and a neutral amino acid substituted at position 51, wherein the ratio of the gastrin derivative to the modified EGF is about 60:1. Yet another embodiment can be a pharmaceutical composition for islet neogenesis therapy (I.N.T.^{TM}), having an effective dose of at least about 1 μg/kg body weight of a modified recombinant EGF and at least about 30 μg/kg body weight of a synthetic gastrin derivative. Yet another embodiment is a pharmaceutical composition for I.N.T.^{TM} <u>islet neogenesis therapy</u> having an effective dose of at least about 1 μg/kg body weight of a modified recombinant EGF and at least about 30 μg/kg body weight of a synthetic gastrin derivative. Yet another embodiment is a pharmaceutical composition for I.N.T.^{TM} <u>islet neogenesis therapy</u>, having an effective dose of at least about 1 μg/kg body weight of a recombinant modified EGF having a deletion of two C-terminal amino acids and a neutral amino acid substituted at position 51, and at least about 30 μg/kg body weight of a synthetic gastrin derivative having a leucine substituted at position 15.

At page 6, lines 7 to 25:

In yet another aspect, the invention provides a method of reducing insulin usage in an insulin-deficient diabetic patient, the method including: administering an effective dosage of an I.N.T.™ islet neogenesis therapy composition, to induce islet neogenesis; and reducing delivery of insulin as islet neogenesis is induced, thereby causing increased insulin secretion and decreased blood glucose. In a related embodiment, the composition comprises a gastrin/CCK receptor ligand and an EGF receptor ligand. The composition can have a gastrin/CCK receptor ligand in an amount that is at least about 10-fold greater in weight than an amount of an EGF receptor ligand in the composition. Administering the composition is performed according to a schedule less than about six months in duration. Further, reducing insulin delivery can be initiated after cessation of administering the composition. Alternatively, reducing exogenous insulin dosing can be initiated within the duration of the schedule of administering the composition. Thus, insulin delivery after administering the composition is reduced to less than about 70% compared to usage in the diabetic patient before administering the composition. For example, insulin delivery after administering the composition is reduced to less than about 50% compared to usage in the diabetic patient before administering the composition; or insulin delivery after administering the composition is reduced to less than about 10% compared to usage in the diabetic patient prior to administering the composition; or insulin delivery after administering the composition is reduced to less than about 1% compared to usage in the diabetic patient prior to administering the composition.

At page 7, lines 10 to 19:

Figure 1 is a graph showing improved glucose tolerance of STZ diabetic rats after treatment by islet neogenesis therapy (I.N.T.™) with gastrin and TGFα, as a function of time. Rat groups are non-diabetic controls (labeled No STZ control n = 4, in the Figure); diabetic STZ mice treated with vehicle only (labeled STZ Vehicle n=12); rats treated with a low I.N.T.™ dosage of 4 μg of each of gastrin and TGFα per kg body weight (labeled STZ 4 TGF/gastrin n=6); and rats treated with 40 μg of each of gastrin and TGFα per kg body weight, a 10-fold higher I.N.T.™ islet neogenesis therapy dosage of each of gastrin and TGFα (labeled STZ 40

TGF/gastrin n=8). The data show that both groups of the I.N.T.™ islet neogenesis therapy treated STZ rats achieved a lower blood glucose level following a challenge than diabetic rats in the untreated control group.

At page 7, lines 20 to 28:

Figure 2 is a bar graph showing increased insulin release in I.N.T.™ islet neogenesis therapy treated rats 15 and 30 min following a glucose challenge. The left set of three bars each drawn as empty bars, stippled bars, and solid bars show plasma insulin levels (ng/ml) in each of the three STZ diabetic rats as in Figure 1. The insulin levels in the non-diabetic rat group at 15 and 30 min following challenge is shown in the bars on the right, on a different scale. The data show that diabetic rats administered the I.N.T.™ islet neogenesis therapy treatment at the high I.N.T.™ islet neogenesis therapy dosage of Figure 1 produce more than three-fold greater insulin than untreated diabetic rats at 15 and 30 min after the challenge, and that rats receiving the low I.N.T.™ islet neogenesis therapy dosage of Figure 1 make more than four-fold more insulin than untreated diabetic rats at 30 min.

At page 7, lines 29 to 33:

Figure 3 is a set of graphs showing blood glucose levels for the groups of rats as in Figure 1, assayed as a function of time, in blood samples taken two weeks after treatment (left panel) and eight weeks after treatment (right panel). The data show that blood glucose in the low dose I.N.T.™ islet neogenesis therapy treated rats remains lower than in untreated controls following a glucose challenge for at least eight weeks following treatment.

At page 8, lines 1 to 5:

Figure 4 is a bar graph showing fasting blood glucose concentration, in mM, in non-diabetic rats (labeled Control), diabetic untreated rats (labeled Vehicle), and rats administered low dosage I.N.T.™ islet neogenesis therapy treatment (labeled TGF/GAS4), at two, four and eight weeks following treatment. Data show that the I.N.T.™ islet neogenesis therapy-treated

rats remain capable of maintaining normal fasting blood glucose levels for at least eight weeks following treatment.

At page 8, lines 6 to 8:

Figure 5 is a graph showing sustained improvement in growth of diabetic I.N.T.™ islet neogenesis therapy-treated rats for at least eight weeks following treatment, compared to untreated diabetic control rats.

At page 8, lines 9 to 14:

Figure 6 is a graph showing fasting blood glucose levels of diabetic rats (labeled Diabetic Control), non-diabetic untreated rats (labeled Non-diabetic Control), and rats administered low dosage I.N.T.™ islet neogenesis therapy treatment (labeled TGF/GAS4), as function of time after treatment (2, 4, 8 and 16 weeks). Data show that I.N.T.™ islet neogenesis therapy-treated rats maintain a lower fasting blood glucose level at least for 16 weeks following treatment, compared to untreated diabetic control rats

At page 10, lines 17 to 34:

Recombinant EGF forms have been genetically engineered to have alterations in structure and activities, for example, EGF having a methionine at position 21 replaced by a leucine residue has been described (U.S. patent number 4,760,023). Recombinant human EGF (hEGF) having 51 residues, i.e., lacking the two C-terminal residues at positions 52 and 53 of hEGF, and having a neutral amino acid substitution at position 51, retain EGF activity and are more resistant to protease degradation during a microbial production process, and following administration to a subject. A series of nucleic acid molecules have been described that encode a family of proteins that have significant similarity to EGF and TGFα (WO 00/29438). EGF muteins (mutated EGF) having histidine at residue 16 replaced with a neutral or acidic amino acid have been described (WO 93/03757), such forms retaining activity at low values of pH. Chemical analogues and fragments of EGF and TGFα retain ability to bind various members of the EGF receptor family

(U.S. patent number 4,686,283). Various modifications of EGF or TGFα confer advantageous properties affecting one or more of recombinant protein production, in vitro and in vivo stability, and in vivo activity. A preferred recombinant modified EGF receptor ligand of the embodiments herein retains substantially full I.N.T.™ islet neogenesis therapy activity, and has in vivo and/or in vitro stability that is that is at least about as great or greater than normal or wild type hEGF.

At page 12, lines 5 to 7:

As used herein, a dosing schedule refers to a protocol for administering an I.N.T.™ islet neogenesis therapy composition, and includes the amount of the composition delivered per day, and the duration or period of time over which the composition is administered.

At page 13, lines 3 to 19:

As a result of administration of the I.N.T.™ islet neogenesis therapy compositions provided herein according to a dosage schedule of such short duration, the process of islet neogenesis is initiated. Precursor cells in the subject are induced to differentiate, and the differentiating cells then mature into islet cells capable of secreting insulin in response to fluctuations in blood glucose levels, i.e., a subject with diabetes enters a period of remission characterized by a normal response to a blood glucose challenge. As a result of this administration, remission of diabetes is initiated, so that the standard dosage of insulin given to a diabetic patient prior to therapy is reduced, as determined by the level of blood glucose obtained by monitoring, for example, by self-monitoring by the patient, during and following treatment. Remission from diabetes due to successful islet neogenesis therapy is indicated by a decreased fasting blood level of glucose, and by a decreased level and duration of elevated blood glucose in response to a dietary challenge of sugar consumption. Upon achieving successful islet neogenesis, insulin administration is reduced from, for example, five injections to two injections per day; from two injections to one injection per day; and from one to none, as indicated by data obtained from monitoring blood glucose levels. One of ordinary skill in the art of pharmacology, when treating a diabetic patient, is familiar with adjusting insulin dosage to levels of blood glucose following fasting and under other physiological conditions.

At page 13, line 20 to page 14, line 2:

Dosages of the I.N.T.™ islet neogenesis therapy compositions to be administered to a subject are adjusted for known variations from species to species in standard data encompassing criteria for absorption, distribution, half-life kinetics in circulation, metabolism, excretion, and toxicology of the receptor ligands of the embodiments herein, for example, for each primate and rodent species. In general, dosages are adjusted to be about 100-fold greater for administration to a rodent species than to a primate species. For example, a dose of an I.N.T.™ islet neogenesis therapy composition for a rat is exemplified by about 3,000 μg/day of a gastrin/CCK receptor ligand and about 100 μg of an EGF receptor ligand, administered for example in three injections per day (for a total of about 9,000 μg of gastrin/CCK receptor ligand and about 300 μg of EGF receptor ligand per day), on a per kg of body weight basis. For a primate such as a cynomolgus monkey, a chimpanzee, or a human, the comparable dose is, for example, about 1 to about 3 μg of EGF receptor ligand, or about 3 to about 10 μg of EGF receptor ligand per kg body weight, and about 30 to about 90 μg, or about 90 to about 300 μg of gastrin/CCK receptor ligand per kg body weight, such daily doses to be administered as a total bolus given once per day, or divided into subdoses to be administered in two or administrations per day.

At page 16, line 5:

Example 1: Prolonged efficacy of I.N.T.™ islet neogenesis therapy compositions and methods in diabetic rats

At page 16, lines 22-29:

Surprisingly, prolonged efficacy of the treatment was observed, with improved glucose tolerance in response to a glucose challenge in the GAS/TGF rats maintained at least to 8 weeks after cessation of treatment (Figure 3). Further, 8 weeks after cessation of treatment, the GAS/TGF treated rats also displayed normal fasting blood glucose levels (6.4 ±1.2 mM) compared to the diabetic levels (12.0 ± 2.2mM) observed in the CON rats (see Figure 4). Rat growth in the I.N.T.™ islet neogenesis therapy-treated groups was normal (Figure 5). The

improved glucose tolerance correlated with improved body weight gain by the GAS/TGF group during the 8 week post treatment period.

At page 16, lines 30-31:

Further, additional data indicate that efficacy of the I.N.T.™ islet neogenesis therapy treatment continues to at least 16 weeks after cessation of the treatment (Figure 6).

At page 17, lines 24-28:

I.N.T.™ islet neogenesis therapy compositions and methods of treatment were performed using groups of STZ rats, using a dosing schedule of 28 days duration, and a composition having gastrin at a weight 30-fold greater than EGF. Rats were administered 100 micrograms/injection of the EGF receptor ligand per kg body weight, and 3 milligrams/injection of gastrin/CCK receptor ligand. Three such injections were administered per day.

At page 18, lines 3-8:

Surprisingly, within 14 days of cessation of treatment with the I.N.T. ™ islet neogenesis therapy composition having a ratio by weight of gastrin/EGF of 30:1, blood glucose levels of a significant number of treated animals were observed to fall within non-diabetic levels. The 30:1 level of gastrin was important to the response since the control group of diabetic rats treated with 3:1 ratio having a 10-fold lower dose of gastrin did not show a significant number of non-diabetic animals at 14 days after treatment.